

Methylglyoxal, the glyoxalase pathway and advanced glycation endproducts in type 2 diabetes and cardiovascular disease

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Valorization

Future directions and applications of the glycation pathways to improve clinical management of T2DM and CVD

Using the glycation pathways to better predict CVD in individuals with and without diabetes

In an ideal situation we would be able to identify individuals at high risk of CVD, and treat them appropriately with risk-modifying medication and life-style changes to reduce their risk before an actual CVD-event takes place. Several risk-markers identify individuals at higher risk of CVD, such as older age, male sex, high blood-pressure, smoking and an unfavorable lipid profile (high LDL-cholesterol, low HDL-cholesterol).⁴⁴ In addition, diabetes itself is a strong risk-factor for CVD. Despite the identification of these risk markers and development of integrated risk-scores to calculate an estimated individual risk of CVD with these variables, it is still very difficult to precisely estimate which individuals will develop CVD and which individuals will remain event free, especially in individuals with diabetes.⁴⁵ As a result, many patients receive insufficient treatment, while others receive treatment from which they do not benefit. Therefore, it is important to study the underlying mechanisms of atherosclerosis, as this may help to identify new risk markers. When these risk markers reflect the underlying disease of a patient these risk markers are called biomarkers. Biomarkers, as measured in blood or urine of a patient, may improve the discrimination between patients with either a high or a low risk of cardiovascular events, which can subsequently be used to improve their treatment. This thesis provides a proof of principle that AGEs measured in the circulation may serve as biomarkers of increased risk of incident CVD. However, the plasma measurements we reported in this thesis displayed some limitations for use in clinical practice, such as associated confounding factors, including obesity. The possibility to measure plasma levels of AGE precursors, protein-bound and free AGEs in circulating cells and free AGEs in urine are all promising and essential steps to translate the findings summarized in this thesis into validated biomarkers which can actually improve risk prediction of CVD. This will be a major focus of future research. Future studies should also investigate the extent to which AGE measurements may serve as biomarkers for risk of microvascular complications of diabetes (retinopathy, neuropathy and nephropathy) in individuals with T2DM. Furthermore, as we identified inflammation and hypoxia as additional sources of AGE accumulation, AGE measurements may also be useful biomarkers in other diseases as well, such as rheumatoid arthritis and chronic obstructive pulmonary disease. In addition to identifying individuals at increased risk of CVD, AGE measurements may identify individuals that would particularly benefit from AGE-

lowering treatments. Such an approach may not only improve the identification of high-risk patients, but also the selection of optimal treatment strategies.

The glycation pathways as potential targets to treat CVD

As we show in this thesis that higher levels of specific AGEs are associated with a higher risk of CVD, it may be worth considering whether reducing AGE levels decrease CVD-risk. Several compounds have been identified that lower AGE levels and/or inhibit AGE formation. The best characterized inhibitor of AGE formation is aminoguanidine.⁴⁶ Administration of this compound has been shown to reduce plaque formation in diabetic ApoE^{-/-} mice.⁴⁰ In addition to AGE- and MGO-lowering properties, aminoguanidine has been described as an antioxidant⁴⁷ and inhibitor of nitric oxide formation.⁴⁸ Likewise, pyridoxamine (a vitamin B6 vitamer) is considered an AGE-inhibitor, with anti-oxidant and anti-inflammatory properties,⁴⁹ and has been shown to reduce atherosclerosis in diabetic ApoE^{-/-} mice.⁴¹ Alagebrium is a compound that has been reported to break pre-existing AGE-crosslinks and has also been shown to lower MGO levels directly.⁵⁰ Indeed, alagebrium has been shown to reduce atherosclerosis in diabetic ApoE^{-/-} mice, although it is unclear if its beneficial effect is attributable to its AGE- or MGO-lowering properties.⁴⁰

Whether these compounds also hold promise as treatment for CVD in humans has still not been determined.⁵¹ Unfortunately, aminoguanidine, when administered to people seemed to induce glomerulonephritis,⁵² and has therefore been deemed unsafe as a drug for humans. Therefore, there still is a need to develop and test new AGE inhibitors. Interestingly, established drugs to treat CVD, such as simvastatin, have also been shown to reduce the accumulation of AGEs in human carotid plaques.⁶ Similarly, several glucose-lowering¹⁶ and antihypertensive compounds³⁴ have also been shown to have AGE-lowering properties. Elucidating whether beneficial effects of these drugs are partly attributable to AGE-lowering is clearly relevant, as most of these drugs been shown to have beneficial effects beyond their glucose-,⁵³ lipid-,⁵⁴ and blood pressure-lowering.⁵⁵ Indeed, these characteristics could perhaps be further exploited by increasing their capacity to decrease AGE levels.

The reduction of dietary intake of AGEs may be an alternative strategy to reduce the risk of CVD. Especially processed foods as well as foods prepared by dry heat are thought to contain high levels of AGEs. Whether a diet low in AGEs or AGE-precursors leads to a reduction in AGE levels in the body is a topic that is currently hotly debated. Experimental studies have shown that the uptake of dietary AGEs is around 10-30%,⁵⁶ and that kidneys rapidly excrete excess free AGE fractions. Therefore, a diet low in AGEs may be particularly useful for patients with kidney failure. In animal studies, a diet low in AGEs reduces insulin resistance and atherosclerosis as well as diabetic neuropathy and nephropathy.⁵⁷ However, randomized clinical trials investigating beneficial effects of dietary regimens low in AGEs are rare, and contain only small

numbers of participants.⁵⁸ Therefore, larger clinical studies on this topic are urgently needed.

Based on findings reported in this thesis, boosting the activity of the glyoxalase pathway does not appear to be an attractive approach to treat CVD. As outlined earlier, we could not show any beneficial effect of GLO1 overexpression on plaque burden or phenotype in ApoE deficient mice. However, before we dismiss the glyoxalase pathway as a promising target in CVD, additional animal studies are needed to investigate the role of GLO1 in plaque regression and specifically to assess mice that are challenged to high MGO levels. An additional interesting direction for future research would be to develop compounds that remove inactivating posttranslational modifications from the GLO1 enzyme. Nevertheless, GLO1 remains an attractive target for diabetic microvascular complications.

In conclusion, the glycation pathways may be promising targets improve both prediction and treatment of CVD, and are therefore deserving of further investigation.

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